586. *A Confirmation of the Structure of 2 : 6-Dimethyl-4-pyrimidylmethyl-lithium and Some Observations on the Condensation of 1 : 3-Diketones with Acetamidine.*

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4-Ethyl-2 : 6-dimethyl- and 2 : 4 : 5 : 6-tetramethyl-pyrimidine have been synthesised by unequivocal methods. Homologation of 2 : 4 : 6-trimethylpyrimidine (*via* the lithium compound) yielded a product whose derivatives were virtually identical with those from 4-ethyl-2 : 6-dimethylpyrimidine thus confirming the structure of 2 : 6-dimethyl-4-pyrimidylmethyl-lithium (Heyes and Roberts, *J.*, 1951, 328).

IN a previous communication (Heyes and Roberts, *J.*, 1951, 328) it was shown that 2 : 4 : 6-trimethylpyrimidine, by reaction with phenyl-lithium, yielded a lithium derivative. This derivative reacted normally with *n*-dodecyl bromide to produce a pyrimidine having a long-chain alkyl substituent. Reduction and hydrolysis of the last-mentioned compound yielded acetaldehyde, proving that the original pyrimidine had not been attacked at the 2-position. The lithium derivative (A) was then formulated, on the basis of theoretical considerations, as 2 : 6-dimethyl-4-pyrimidylmethyl-lithium and the final product (B) as 2 : 6-dimethyl-4-*n*-tridecylpyrimidine. It was suggested by one of the referees of the above paper that an alternative structure for A, 2 : 4 : 6-trimethyl-5-pyrimidyl-lithium (and hence a structure 5-*n*-dodecyl-2 : 4 : 6-trimethylpyrimidine for B), could not be ignored. Although, from a theoretical standpoint (*loc. cit.*; see also Roberts, *Chem. and Ind.*,1947, **66**, 658), we considered these alternative structures to be very unlikely it was thought desirable, before proceeding with further work in this field (forthcoming paper by Heyes and Roberts), to produce experimental confirmation of the original formulations. This paper describes the work undertaken for this purpose.

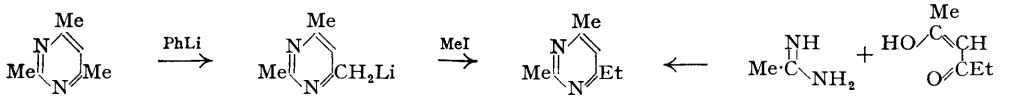
Although it was realised that many pyrimidines can readily be nitrated in an initially unsubstituted 5-position, no attempt was made to confirm the structure of B (and hence of its precursor, A) by this method since it is known (Gabriel and Colman, *Ber.*, 1902, **35**, 1570) that certain 4(6)-methylpyrimidines are attacked by nitric acid to yield furazan derivatives. Two methods for confirming the structure of A were explored but only one proved successful.

In the first there was envisaged a proof of the structure of A by identification of the oxidation product produced from its derivative B. This would have been pyrimidine-2 : 4 : 6-tricarboxylic acid or, if A and B had had the alternative structures mentioned above, pyrimidine-2 : 4 : 5 : 6-tetracarboxylic acid. Of these two acids the former had been previously characterised (Kondo and Yanai, *J. Pharm. Soc. Japan*, 1937, **57**, 173; *Chem. Zentr.*, 1938, II, 858) and it was thought that the structure of the latter could have been confirmed through its conversion into pyrimidine-5-carboxylic acid by partial decarboxylation (cf. Gabriel and Colman, *Ber.*, 1904, **37**, 3647). However, experiments on 2 : 4 : 6-trimethylpyrimidine indicated that the oxidation of such alkylpyrimidines (by means of potassium permanganate) was exceedingly slow. After a reaction period of 33 hours the only pure product isolable was a methylpyrimidinedicarboxylic acid, m. p. 196° (decomp.), which is probably 6-methylpyrimidine-2 : 4-dicarboxylic acid (cf. Ochiai and Yanai, *J. Pharm. Soc. Japan*, 1938, **58**, 76; *Chem. Zentr.*, 1938, II, 4242). This approach was abandoned.

The second method consisted in conversion of 2 : 4 : 6-trimethylpyrimidine (*via* its lithium derivative) into its next higher homologue and comparison of the latter with the known 4-ethyl-2 : 6-dimethyl- and 2 : 4 : 5 : 6-tetramethyl-pyrimidine. The material produced by homologation could not be obtained analytically pure * but it yielded derivatives (a picrate, a picrolonate, and a double compound with mercuric chloride) which were

* This material was probably contaminated with, *inter alia*, some 4 : 6-diethyl-2-methylpyrimidine; cf. the production of some 2-methyl-4 : 6-di-*n*-tridecylpyrimidine as a by-product in the preparation of 2 : 6-dimethyl-4-*n*-tridecylpyrimidine (Heyes and Roberts, *J.*, 1951, 330).

virtually identical with the corresponding derivatives prepared from 4-ethyl-2 : 6-dimethylpyrimidine. The following reactions were thus established :



The structures of 2 : 6-dimethyl-4-pyrimidylmethyl-lithium and 2 : 6-dimethyl-4-*n*-tridecylpyrimidine are, therefore, confirmed.

Condensation of 1 : 3-*Diketones with Acetamidine.*—Previous attempts to condense a 1 : 3-diketone with an amidine appear to have been limited almost entirely to the use of acetylacetone. [Pinner found that formylacetone would not condense with benzamidine (*Ber.*, 1893, **26**, 2122). Valerylacetone and urea are stated to produce diuramidovalerylacetone and not the expected pyrimidine (Yanai and Naito, *J. Pharm. Soc. Japan*, 1941, **61**, 46; *Chem. Zentr.*, 1942, I, 483).] It is now shown that propionylacetone will condense with acetamidine under conditions similar to those described by Bowman for acetylacetone (*J.*, 1937, 494; *cf.* Kondo and Yanai, *loc. cit.*)—conditions which are probably optimum for condensations of this type (Haley and Maitland, *J.*, 1951, 3160). The condensation gave a moderate yield of the desired 4-ethyl-2 : 6-dimethylpyrimidine. Methylacetylacetone (3-methylpentane-2 : 4-dione) and acetamidine yielded a small quantity of 2 : 4 : 5 : 6-tetramethylpyrimidine which was purified and identified as the picrate.

The condensation of acetylacetone and acetamidine, by Bowman's method, was found to yield not only 2 : 4 : 6-trimethylpyrimidine but also a considerable quantity of acetylacetone imine. By a similar process propionylacetone yielded the corresponding pyrimidine and, as a by-product, an appreciable quantity of a monoimine of propionylacetone whose exact structure was not determined. In the condensation of methylacetylacetone with acetamidine there was no evidence for the production of a corresponding imino-compound.

Experimental

2 : 4 : 6-*Trimethylpyrimidine.*—Acetylacetone (77 g.) was condensed with acetamidine by Bowman's method. The crystalline hydrate was filtered off. The filtrate was saturated with anhydrous potassium carbonate (300 g. required) and was then extracted with ether (3 × 100 c.c.). To the mixture of the ethereal extract and the crystalline hydrate was added, with occasional vigorous shaking, just sufficient anhydrous potassium carbonate to give two clear liquid layers. The ethereal solution was separated, dried (K_2CO_3, 25 g.) and filtered. The solvent was evaporated and the residue distilled at 12 mm. Three fractions were collected : (i) b. p. $<62°$ (1 g.); (ii) b. p. 62—90° (18·6 g.); (iii) b. p. 94—120°, (9·5 g.). Fraction (ii) was redistilled and yielded, as a middle fraction, 12·2 g. of 2 : 4 : 6-trimethylpyrimidine, b. p. 68—72°/11·5 mm. (Kondo and Yanai, *loc. cit.*, give b. p. 80—84°/16 mm.), 168—170°/745 mm. [Bowman, *loc. cit.*, gives " b. p. 160° (approx.) "].

Fraction (iii) from the first distillation partly solidified at room temperature. It was kept at −2° overnight and the crystalline portion was then separated by filtration from some contaminating dark oil. The crystals were well washed with light petroleum (b. p. 40—60°) and dried (3·1 g.; m. p. *ca.* 34°) at room temperature in a vacuum over concentrated sulphuric acid. Distillation *in vacuo* of this crystalline material yielded a fraction, b. p. 98—99°/11·5 mm. (1·4 g.), which solidified in the condenser to a mass of colourless prisms. This substance, m. p. 39—40°, was readily soluble in water, ethanol, and benzene; it gave a dark-red ferric reaction in ethanol and was identified as acetylacetone imine (2-aminopent-2-en-4-one) (Found : C, 60·7; H, 9·0; N, 13·9. Calc. for C_5H_9ON : C, 60·6; H, 9·2; N, 14·1%) (Combes and Combes, *Bull. Soc. chim.*, 1892, **7**, 779, give m. p. 43°).

Oxidation of 2 : 4 : 6-*Trimethylpyrimidine with Potassium Permanganate.*—A solution of the pyrimidine (1·0 g.) in water (50 c.c.) was gently boiled under reflux with vigorous mechanical stirring. An aqueous solution of potassium permanganate (2% w/v) was added at a rate such that there was always a slight excess of the oxidising agent in the reaction mixture. During 33 hours 350 c.c. of the permanganate solution were added. Reaction then appeared to be complete. The manganese dioxide was filtered off and washed thoroughly. The pH of the combined filtrate and washings was adjusted to 8·5—9·0 by the addition of dilute sulphuric acid, and the solution was then evaporated to 150 c.c. After filtration to remove a little manganese

dioxide and some gelatinous matter, the solution was strongly acidified (pH <1) with dilute sulphuric acid and set aside overnight. The crystalline precipitate was filtered off, washed with water, and dried [0·48 g.; m. p. 197° (decomp.)]. Recrystallisation from boiling water yielded 6(or 2)-methylpyrimidine-2(or 6) : 4-dicarboxylic acid as colourless, microscopic prisms which were dried (0·35 g.) *in vacuo* over concentrated sulphuric acid. The m. p. (with decomp.) of the dihydrate, thus prepared, varied with the rate of heating from 196° (slow heating) to 208° (rapid heating) (Found : C, 38·7; H, 4·8; N, 12·9%; equiv., by titration, 107·6. Calc. for $C_7H_6O_4N_2,2H_2O$: C, 38·5; H, 4·6; N, 12·8%; equiv., 109·1). An aqueous solution of this acid was coloured wine-red by the addition of a solution of ferrous sulphate. Ochiai and Yanai (*loc. cit.*) record the m. p. of " 6-methylpyrimidine-2 : 4-dicarboxylic acid " (in the form of the dihydrate) as 195—197° (decomp.).

By evaporation of the neutralised mother-liquor of the foregoing acid, followed by acidification, there was obtained a further quantity of crystalline acidic material (*ca.* 0·18 g.) which, when heated, gradually decomposed over the range 190—360° and probably consisted of a mixture of the dicarboxylic acid with pyrimidine-2 : 4 : 6-tricarboxylic acid. This material was not further investigated.

4-*Ethyl*-2 : 6-*dimethylpyrimidine*.—A mixture of a solution of anhydrous potassium carbonate (27·6 g., 2 mols.) in water (90 c.c.) and propionylacetone (11·4 g., 1 mol.) [prepared by the method of Morgan and Reeves (*J.*, 1923, **123**, 447)] was not homogeneous after having been vigorously shaken. Acetamidine hydrochloride (9·45 g., 1 mol.) was added and the mixture was vigorously shaken, in a tightly-stoppered vessel, for 20 hours. After being kept at room temperature, with intermittent shaking, for 26 days the mixture was saturated with anhydrous potassium carbonate (*ca.* 60 g. required) and extracted with ether (45 + 45 + 30 c.c.). The combined ethereal extracts were washed with water (15 + 10 c.c.) and then extracted thoroughly with 2N-sodium hydroxide (40 + 40 + 30 c.c.) in order to remove any unchanged diketone. The ethereal layer was washed with water (10 c.c.), dried (Na_2SO_4, 20 g.), filtered, and evaporated to about 15 c.c. This concentrated solution, after being kept over pellets of potassium hydroxide (1 g.) for 20 minutes, was filtered through an alkali-resistant filter-paper and the ether was evaporated. The residue, when distilled *in vacuo*, yielded fractions (i) b. p. 72—76°/11 mm. (1·6 g.), and (ii) b. p. 102—104°/11 mm. (*ca.* 0·5 g.).

The first fraction, 4-*ethyl*-2 : 6-*dimethylpyrimidine* (Found, on a redistilled specimen : C, 70·9; H, 8·9; N, 20·3. $C_8H_{12}N_2$ requires C, 70·6; H, 8·9; N, 20·6%), was a colourless, mobile, volatile, hygroscopic oil with an intense odour somewhat resembling that of impure acetamide. It was soluble in water and in the common organic solvents.

This pyrimidine (0·3 g.) was gently warmed with picric acid (0·5 g.) in 95% ethanol (3·5 c.c.), until a clear solution was obtained. After being cooled and " scratched " the solution deposited 0·50 g. of crude material, m. p. 85—87°. Recrystallisation from 95% ethanol (1·7 c.c.) yielded the pure *picrate* (0·04 g.), lemon-yellow prisms, m. p. 86—87° (Found : N, 19·3. $C_8H_{12}N_2,C_6H_3O_7N_3$ requires N, 19·2%), very readily soluble in water, ethanol, and benzene. The *picrolonate* separated from ethanolic solution as a yellow micro-crystalline powder, m. p. 191° (decomp.) (Found : N, 21·2. $C_8H_{12}N_2,C_{10}H_8O_5N_4$ requires N, 21·0%). An aqueous solution of the pyrimidine, after being mixed with a solution of mercuric chloride, slowly deposited silky needles of the double *compound*, m. p. 103—104° (Found : N, 4·2. $C_8H_{12}N_2,2HgCl_2$ requires N, 4·1%).

The second fraction from the distillation crystallised in the condenser. The crystals were collected, washed well with light petroleum (b. p. 40—60°), and dried (*ca.*, 80 mg.; m. p. 58—60°). Recrystallisation from light petroleum (b. p. 40—60°) yielded 2-aminohex-2-en-4-one (or 3-aminohex-3-en-5-one) as colourless prisms, m. p. 62° (Found : C, 64·1; H, 9·3; N, 12·1. Calc. for $C_6H_{11}ON$: C, 63·7; H, 9·8; N, 12·4%). This material was sparingly soluble in water and light petroleum and gave a dark-red ferric reaction in ethanol. (Küster, *Chem. Zentr.*, 1925, I, 2080, records m. p. 49° for 2-aminohex-2-en-4-one.)

2 : 4 : 5 : 6-*Tetramethylpyrimidine Picrate*.—A mixture of a solution of anhydrous potassium carbonate (29·8 g., 2 mols.) in water (100 c.c.) and methylacetylacetone (12·3 g., 1 mol.) (Perkin, *J.*, 1892, **61**, 848) was not homogeneous after having been vigorously shaken. Acetamidine hydrochloride (10·2 g., 1 mol.) was added and the mixture was vigorously shaken for 24 hours. After being kept at room temperature, with occasional shaking, for 7 weeks the mixture was saturated with potassium carbonate (*ca.* 70 g.), and the crude product was isolated by the method described for 4-ethyl-2 : 6-dimethylpyrimidine. The residue (1—2 c.c.), produced by evaporation of the dried ethereal extract, was distilled *in vacuo*. A brown oil (0·5 g.) slowly distilled at 82—122°/20 mm. (The distillation was too slow for an accurate estimation of b. p.

to be made.) The odour of this oil was very similar to that of 4-ethyl-2 : 6-dimethylpyrimidine. To a warm (60°) solution of this oil (0·5 g.) in 95% ethanol (3 c.c.) was added a warm solution of picric acid (0·75 g.) in 95% ethanol (6 c.c.). The solution, having been cooled, " scratched " and allowed to stand overnight at −2°, deposited greenish-yellow crystals which were filtered off, washed and dried (0·7 g., m. p. 117—128°). This material, after three recrystallisations from ethanol (95%), yielded 2 : 4 : 5 : 6-*tetramethylpyrimidine picrate* (0·48 g.) as deep-yellow prisms, m. p. 129—130° [Found : C, 46·6; H, 4·1; N, 19·3; picric acid (by precipitation as nitron picrate, Busch and Blume, *Z. angew. Chem.*, 1908, **21**, 354), 62·6%. $C_8H_{12}N_2,C_6H_3O_7N_3$ requires C, 46·0; H, 4·1; N, 19·2; picric acid, 62·7%].

Homologation of 2 : 4 : 6-*Trimethylpyrimidine.*—A phenyl-lithium solution was prepared from bromobenzene (15·7 g., 1 mol.), lithium chips (1·42 g., 2·04 atomic equivs.), and dry ether (70 c.c.) under nitrogen. To the ice-cold solution was slowly added, with mechanical stirring, 2 : 4 : 6-trimethylpyrimidine (12·2 g., 1 mol.) in dry ether (25 c.c.). The mixture was stirred for 15 minutes at room temperature and was then cooled in a freezing-mixture. Methyl iodide (15·6 g., 1·1 mols.) in dry ether (10 c.c.) was slowly added with vigorous stirring. The greenish-yellow sludge of the lithium derivative gradually disappeared. The mixture was boiled under reflux for 2 hours. After being kept overnight at room temperature the mixture was vigorously stirred with water (40 c.c.). The lower layer, after being extracted with ether (20 c.c.), was discarded. The combined ethereal solutions were extracted with 2N-hydrochloric acid (60 + 40 + 20 c.c.). To the combined acid extracts was added, with cooling, a solution of sodium hydroxide (12 g.) in water (40 c.c.), whereupon a yellow oil separated. The mixture was extracted with ether (100 + 50 c.c.), and the ethereal extract washed with water (20 c.c.), dried ($MgSO_4$, 8 g.), and filtered. After evaporation of the ether the residue was distilled at 13 mm. and yielded fractions (i) b. p. 73—77° (0·55 g.), (ii) b. p. 77—81° (3·1 g.), and (iii) b. p. 82—86° (0·85 g.). The middle fraction was used for preparing the following derivatives. 0·3 G. of the base, when treated as described for 4-ethyl-2 : 6-dimethylpyrimidine, yielded 0·45 g. of crude picrate, m. p. 85—87°. Recrystallisation from 95% ethanol gave 0·33 g. of lemon-yellow prisms (Found : N, 19·1%), m. p. 87—88° alone, or, after admixture with an authentic specimen of 4-ethyl-2 : 6-dimethylpyrimidine picrate, 87°.

The picrolonate separated from ethanolic solution as a microcrystalline, yellow powder, m. p. 192° decomp.).

The double compound with mercuric chloride separated from water in silky needles, m. p. 105° alone, or, after admixture with an authentic specimen of the double compound from 4-ethyl-2 : 6-dimethylpyrimidine, 104—105°. (The m. p.s of these double compounds with mercuric chloride vary with their " age." The constants quoted above were for specimens of " age " one day.)

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